UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/555,664	11/04/2005	Peter Assaf	30724	9895

7590 01/04/2008

Martin Moynihan
Prtsi Inc
PO Box 16446
Arlington, VA 22215

EXAMINER	
LOEWE, SUN JAE Y	
ART UNIT	**PAPER NUMBER**
1626	

MAIL DATE	DELIVERY MODE
01/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/555,664	ASSAF ET AL.	
	Examiner	Art Unit	
	Sun Jae Y. Loewe	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *2,3,7,12-15,18-27,30,31 and 34-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-11,16,17,28,29,32,33,65-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-28-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

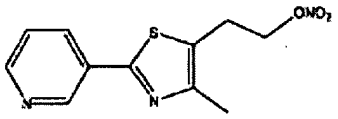
DETAILED ACTION

1. Claims 1-75 are pending in the instant application.

Election/Restrictions

2. An election of species requirement for Groups I, III and V (restriction requirement dated October 9, 2007) was inadvertently not made. An election of species requirement is made herein for Groups I, III, and V. The species lack unity of invention for the reasons discussed in sections 5-7 of the previous restriction requirement.

3. Applicant's election with traverse of Group I, and species Pet-12 (structure below), in the reply filed on November 7, 2007 is acknowledged.



The traversal is on the ground:

> The different structure of the compound taught in Silberg et al. therefore renders this compound structurally and conceptually different from the compounds of the instant application in more than one aspect.

The difference in the structure of the prior art compound is noted. However, it is maintained that this compound shares the same core structure as the instantly claimed Markush group of Formula I, ie. a thiazole ring. Therefore, Groups I-VI, and the species encompassed of Formula I, lack unity of invention.

The restriction requirement between Groups I-VI is still deemed proper and is hereby made FINAL.

4. MPEP 1893.03(d) states that when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. See excerpts below:

> Note: the determination regarding unity of invention is made without regard to whether a group of inventions is claimed in separate claims or as alternatives within a single claim. The basic criteria for unity of invention are the same, regardless of the manner in which applicant chooses to draft a claim or claims.
>
> >If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any non-

The elected species of Pet-12 was not allowable under 35 U.S.C 112 (see below section 10). Notwithstanding the non-allowability of the elected species, in the interest of expediting prosecution, the following non-elected species were rejoined and examined herein: compounds encompassed by Group I wherein X=pyridinyl. Multiple species within this subgenus were found to be non-allowable (see Sections 9 and 10).

In view of the above, the scope of the search and examination was limited to:

X= pyridinyl

A=

alkenyl, alkoxy, alkyl, alkynyl, amine, C-amide, carbonyl, C-carboxylate, cycloalkyl, diazo, disulfide, guanidine, guanyl, haloalkyl, hydrazine, N-amide, N-carbamate, nitro, O-carbamate, O-carboxylate, oxygen, sulfur, or absent; cyclic substituents (eg. heteroaryl, aryl, aryloxy) limited to benzodioxole, diazole, piperidine, pyridine, thiazole, pyrazine, dithiolane, furan, thiophene, benzothiophene, pyrrolidine, quinoline, phenyl, naphthyl.

B= unsubstituted alkylene chain or unsubstituted alkylene interrupted by one heteroatom
Y= $-ONO_2$
Z= hydrogen or unsubstituted alkyl

Non-elected species outside of the subgenus defined above are patentably distinct and are not rejoined.

5. Claims 2, 3, 7, 12-15, 18-27, 30-31 and 34-64 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter. Applicant timely traversed the restriction requirement between Groups I-VI in the response dated November 7, 2007.

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

7. The information disclosure statement (IDS) submitted on February 28, 2007 was filed in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is enclosed herewith.

Claim Objections

8. Claims 1, 4-6, 8-11, 16, 17, 28, 29, 32, 33 and 65-75 objected to for containing non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4-6, 8-11, 16, 17, 28, 29, 33 and 65-75 rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. ***Scope of Claims (based on searched and examined subject matter)***

Compounds of Formula I with the structural limitation defined in Section 4.

The following variables are claimed *broader* than what is supported by the disclosure (see below section II):

B: for all claims except claims 10, 11, 16 and 17

A: for all claims

II. ***Scope of Disclosure***

Reduction to Practice:

The compounds reduced to practice support the following definitions for the variables noted above.

B: unsubstituted alkylene chain

A: absent, amide, amine, alkylene-amine (based on methylene amine)

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of *lists* of possible groups (eg., pyrrole, furane, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, for heteroaryl). This type of disclosure is not a representation of any of the species it entails. A"laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. Thus, it is not understood what *specific structural elements* allow for preservation of the claimed activity in compounds within the unrepresented genus.

III. *Analysis of Fulfillment of Written Description Requirement:*

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC_{50} and/or EC_{50} data of multiple compounds with various types of structural

modifications. These types of studies provide insight into the structural limitations that are required for activity, ie. specific structural elements essential for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1, 4-6, 8-11, 16, 17, 28, 29, 33 and 65-75; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

10. Claims 1, 4-6, 8-11, 16, 17, 28, 29, 32, 33 and 65-75 rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for:

a) The intended use of "decreasing a development of tolerance to the NO-donating compound" (see pg. 6, 7 and 148);

b) Making/using compounds that have written description support in the disclosure (see above Section 9.II).

The specification is not enabling for:

aa) The intended use of "preventing a development of tolerance to the NO-donating compound";

bb) Using compounds that do not have written description support in the disclosure (see above Section 9.II.)

Thus, the specification does not enable one of ordinary skill in the art to practice the invention commensurate in scope with the claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

The breadth of the claims

aa) Compounds not supported by the disclosure (see above section 9.I and 9.II.).

bb) Claimed intended use: NO-donating compounds that prevent a development of tolerance to the NO-donating compound.

The nature of the invention

aa) The compounds are disclosed to be nitric oxide donors. An alternate utility is neither disclosed in the specification nor known in the art for this genus of compounds.

bb) The specification discloses in vitro studies that show that the activity (based on measured cGMP levels) of the instantly claimed compounds in pre-infused aortic tissue is not significantly different the activity in post-infused aortic tissue.

The state of the prior art/level of ordinary skill/level of predictability

aa) The level of ordinary skill is high, but the level of predictability in the art is low. Limited SAR is reported for the instantly claimed genus of compounds (ie. subgenus defined in Section 4) - see specification p. 143-151. Furthermore, SAR studies have been disclosed for other compounds that have the same utility as instantly claimed. See demonstrative excerpts below:

- Instant disclosure, page 146 Table 3:

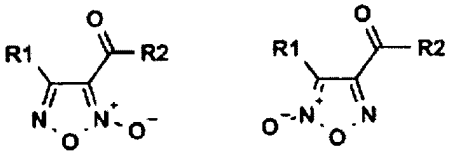
Table 3

Compound	Concentration	EC_{50}	Figure No.
GTN	4.47E-08	-7.55	3 to 6 and 8 to 14
Pet-2	2.51E-08	-7.6	2 and 3
Pet-3	3.55E-08	-7.45	4
Pet-7	2.82E-08	-7.55	5
Pet-8	2.82E-08	-7.7	6
Pet-12	3.98E-08	-7.4	7
Pet-24	2.00E-07	-6.7	8
Pet-43	1.59E-07	-6.8	9
Pet-59	7.94E-08	-7.1	10
Pet-147	3.16E-08	-7.5	11
Pet-152	5.01E-08	-7.3	12
Pet-154	3.98E-08	-7.4	13

It is noted that the compounds above have B=unsubstituted ethylene.

- Schonafinger, Table 1:

Table 1
Furoxanes: isolated guinea pig pulmonary artery



R1	R2	IC-50 (μM)	IC-50 (μM)
$-CH_3$	$-NH_2$	2.9	> 100
$-CH_2CH_2CH_3$	$-NHCH_2CH_2N^iPr_2$	9.5	32.0
$-CH_2-OH$	$-NH_2$	12.0	> 100
3-Pyridyl	$-NHCH_3$	0.7	4.0
$4-NO_2-Ph$	$-NHCH_2CH_2N^iPr_2$	0.04	–
$-CONH^iPr$	$-NH^iPr$	0.07	0.07
$-CONEt_2$	$-Net_2$	> 100	> 100

As discussed in section 9, it is not known what structural limitations are required for preservation of activity within the unrepresented genus. In view of the low level of predictability, as evidenced by the examples above, one of ordinary skill would not know what structural modifications would lead to compounds that have the claimed activity.

bb) The level of predictability in modulating tolerance is low. The following demonstrate the state of the art:

- Multiple mechanisms underlie time- and dose-dependent tolerance (instant specification pg. 6);

- Drug tolerance presents the most challenging limit for the clinical use of organic nitrite and nitrate esters (instant specification pg. 5);
- Nitrate tolerance induced by the administration of nitroglycerin (an NO donor) is observed in situations where NTG is administered long term in vivo and is not induced by short-term exposure of vascular segments in vitro (Munzel, p. 1103).

The instant specification provides support for in vivo short term induced tolerance. These studies, in view of the low level of predictability, are not indicative to prevention of a development of tolerance - ie. one set of experimental conditions is not indicative of all experimental conditions (as encompassed by the term "prevent").

The amount of direction provided by the inventor/existence of working examples

aa) Direction and working examples are limited to the making/using of compounds that have written description support (see Section 9.II).

bb) Direction/guidance is limited and cannot be extended to support the full scope of claim supra.

The quantity of experimentation needed to make or use the invention

aa) It is not known which of the unrepresented compounds meet the structural requirements for activity. Thus, one of ordinary skill would not be enabled by the disclosure to make/use the claimed NO-donors. The amount of experimentation needed to practice the invention commensurate in scope with the claims is undue. Further, absent an alternate utility, one of ordinary skill would not be enabled to use the compounds within the genus that are not adequately supported.

bb) In view of the low level of predictability, one of ordinary skill is not enabled by the instant disclosure to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 32 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim refers to Table 1 and Table 2. Claims must stand alone to define the invention and incorporation by express reference to specification and/or drawings is not permitted. One must refer back to the specification to determine what Applicant is claiming by the express reference to the tables. It is suggested that Applicant insert the data from the appropriate tables into the claims.

12. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim refers to the terms "residue" and " naturally occurring metabolite ". These terms render the claim indefinite because the metes and bounds cannot be ascertained. These structural limitations were not further examined herein.

Conclusion

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sun Jae Y. Loewe, Ph.D.
Patent Examiner
Art Unit 1626

Kamal Saeed, Ph.D.
Primary Examiner
Art Unit 1626